

EDITORIAL COMMENT

Visualizing Vulnerability

Toward a New Cardiac Score*

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Coronary artery disease is almost ubiquitous in our population but comes in a wide variety of shapes and sizes. For decades, a simple but powerful concept has guided decision making in prescribing therapies: the highest risk forms of the disease require the most aggressive treatments, whereas the lowest risk forms warrant only the most gentle. That is, the patient with 3-vessel disease and left ventricular dysfunction requires bypass surgery, whereas the patient with minimal coronary irregularities requires only a statin or aspirin. Even within the context of patients receiving medical therapy without revascularization, a wide range of treatments are now or will soon be available, including aspirin, mild or strong P2Y₁₂ inhibitors, statins, and PCSK9 inhibitors to moderate or low low-density lipoprotein targets, interventions to augment high-density lipoprotein, antihypertensive

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drugs to various levels of BP reduction, angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers, and drugs to inhibit vascular inflammation. To prescribe individualized therapy, we need an accurate assessment of risk. The study by Versteysen et al. (1) in this issue of the *Journal* demonstrates that quantitative information derived from the direct imaging of atherosclerotic lesions by computed tomography angiography (CTA) has the potential to define risk more accurately and therefore guide therapy in a way that has previously not been possible.

A large body of literature has accumulated in which characteristics of an individual plaque susceptible to rupture or erosion (2) with subsequent thrombus formation are defined, with the thought that these plaques might be detected by imaging methods and treated by catheter-based therapy before they precipitate an ischemic event. At autopsy, histologic characteristics of such vulnerable plaques, called thin-cap fibroatheromas, include the presence of

a large necrotic core and a thin (<65 μ m) fibrous cap weakened by infiltration with macrophages (2). During life, thin-cap fibroatheromas may be detected invasively using virtual histology (VH) intravascular ultrasonography (IVUS), which displays them as plaques with lipid adjacent to the lumen. The PROSPECT study determined that plaques with the VH thin-cap fibroatheromas pattern, plaque burden >70%, and maximal luminal area <4 mm² were most likely to lead to events. Other invasive techniques are under development and study, such as near-infrared spectroscopy (3), in which the arterial wall is interrogated for lipid deposits, and optical coherence tomography (4), in which reflected light generates high-resolution images of superficial layers of the vessel wall. Noninvasively, by CTA, visualized vulnerable plaque features include low-attenuation (HU <30) sometimes in a “signet ring pattern” (5), positive remodeling, and spotty calcification (6).

Yet, it is unlikely that any approach based on the detection of individual vulnerable plaques will bear clinical fruit in the foreseeable future (7). Most plaque disruptions are silent events. Even if thrombus forms, in most cases there is no luminal obstruction (8–10) and no ischemia, and the disruption merely results in unnoticed plaque growth. Furthermore, serial study by IVUS suggests that noncalcified plaque with vulnerable characteristics by VH-IVUS may evolve into a more stable appearance and vice versa, even in a period as short as 12 months (11). Therefore, even if new imaging techniques are successful in more accurately identifying plaques that may rupture, any attempt at catheter-based therapy would need to be applied to many, many sites before a single event is prevented.

The solution is to consider the vulnerability of the entire patient rather than that of the individual plaque. This allows the taking into account of susceptibility of the patient to thrombosis (7,12). In addition, the obvious other factor to consider is the total quantity of high-risk plaque material, which determines the probability that plaque disruption will occur at some unknown site or other. Ideally, there would be a global vulnerable plaque “score” analogous to the calcium score, but sensitive to the plaque characteristics that are directly responsible for ischemic events rather than to calcium, an indirect marker of disease activity. To have the greatest impact, our efforts at defining vulnerability should be focused on determining patient risk with a thrombosis/plaque score so that systemic rather than local therapy of appropriate aggressiveness can be applied. The high-scoring patient would need the strictest low-density lipoprotein and blood pressure management, the strongest antiplatelet regimen, and the broadest blockade of the renin-angiotensin system. Future therapies that are successful at reducing residual risk with treatment directed at high-density lipoprotein (13) and suppression of inflammation (14) might also be heaped upon this unfortunate patient. The patient with a low score might be adequately protected with an aspirin alone.

Versteysen et al. (1) have made progress toward this personalization of risk assessment by following up 1,650

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.

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patients with stable chest pain who had undergone cardiac CTA for an average of 26 months and comparing the 26 patients who had an acute coronary syndrome (ACS) with 101 controls with coronary artery disease randomly selected from the non-ACS group. Coronary arteries were evaluated with a whole-heart quantitative technique, using a commercially available software package that draws contours along plaques of different densities and allows quantification of global and maximal plaque characteristics. Several similar packages are on the market and have been validated by comparison to IVUS (15,16). The investigators found that the most predictive global parameters were the total volume of noncalcified plaque, the total volume of all plaque, and the total number of plaques. The most predictive local parameters were the presence of plaque with the highest volume, and lesions with the highest plaque burden. Receiving honorable mention were plaques with the highest area, the highest noncalcified percentage, the lowest attenuation, and the highest remodeling index. These findings are consistent with the well-accepted concept that noncalcified plaque is the usual culprit and that calcified plaque is a marker only of disease burden and not a major player in the mechanism of acute ischemic events. This work confirms and extends the findings of Kristensen et al. (17), who showed that in post-ACS patients (a higher risk population than that studied here) multivariate analysis yielded the same 2 parameters as the major determinants of prognosis: noncalcified plaque volume and total plaque volume. Therefore, it appears that elements of a new scoring system should certainly include total volume of noncalcified plaque and maximal volume or plaque burden of an individual plaque.

One new contribution of Versteyle et al. (1) is the finding that these parameters can be measured semi-automatically, which brings an otherwise time-consuming measurement a step closer to clinical utility. The authors did not describe the average time to make and edit these measurements. The software that requires the least human correction to correspond with a visual assessment, and that provides tools for the fastest editing, will prevail here.

Conventional interpretation of CTA includes calcium scoring, a description of plaques and their characteristics, and an assessment of stenosis with designation as nonobstructive, 1-, 2-, or 3-vessel disease (18). Versteyle et al. (1) here demonstrate that this new type of quantitative analysis provides prognostic information that improves upon conventional interpretation of CTA: the area under the receiver-operating characteristics curve for predicting events was increased from 0.64 to 0.79 when these new quantitative parameters were applied. These data suggest that the multiple studies showing accurate prediction of prognosis by cardiac CT using conventional interpretation (19–22) have not yet fully tapped the power of the technique. For example, the CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry) study has provided multicenter prospective data in 24,775 patients, showing decreasing survival in nonobstructive versus

1-vessel obstructive, versus 2-vessel obstructive, and versus 3-vessel obstructive disease—an analysis relying on old-fashioned “lumenography” rather than on plaque within the arterial wall (23). Although a semiquantitative “segment involvement score” (SIS) also was reported, a more quantitative assessment of noncalcified plaque in that and other large datasets is likely to provide new insights.

Coronary artery calcium (CAC) scoring has greatly refined our ability to predict risk in the asymptomatic population, and it now carries a IIa guideline recommendation for patients at intermediate Framingham risk score, in which half can be correctly reclassified into high or low categories (24). The guidelines give a IIb recommendation for patients at low to moderate risk. Now that CTA can be performed with a radiation dose comparable to that of calcium scoring (25), would a risk score based on noncalcified plaque provide better classification of asymptomatic patients? Choi et al. (26) followed up 1,000 asymptomatic patients and did not find an advantage of CT angiography over CAC for screening, but theirs was a very low-risk population and only 15 events, including only 1 ACS, occurred during the 17 months of follow-up reported. Recent findings from the CONFIRM registry also suggest no advantage of CTA over CAC in 7,590 subjects from this population (27), but this was a conventional CT analysis that did not include noncalcified plaque volumes or other global parameters introduced more recently. Perhaps this result would change if the data were reanalyzed with these measurements included. However, from a practical point of view, the simplicity, speed, and low cost of calcium imaging will make it hard to beat as a screening tool for low-risk populations. It is in higher risk populations, such as patients with stable angina, where CT angiography with conventional interpretation is already known to predict adverse outcomes (19–22,28). In post-ACS patients, the augmented power of plaque-scored CTA may become evident. Calcium scoring has little role in these populations.

Availability of a plaque score may resolve some fundamental contradictions in cardiology. For instance, we clinicians pay lip service to the fact that most ischemic events result from disruption of nonstenotic plaques (12), yet we manage patients on the basis of single-, double-, or triple-vessel stenotic disease. The true importance of stenosis versus plaque volume is unknown. While it is true that CT studies (20) have confirmed catheterization studies showing a major difference in prognosis between nonobstructive, single-, double-, and triple-vessel disease, multivessel patients have more nonobstructive plaque as well, which could be the real determinant of prognosis. An outcome study reporting both plaque measures and stenosis could reveal whether 1 or both aspects of the disease have an independent prognostic effect.

Another issue needing clarification is how to select the optimal method for revascularization when it is deemed to be necessary. We currently decide whether to use percutaneous coronary intervention versus coronary artery bypass graft surgery on the basis of technical features, the

anticipated likelihood of restenosis, the angiographic load of disease, and other factors captured by the score based on the SYNTAX (Synergy Between PCI With TAXUS and Cardiac Surgery) study (29). Wouldn't it make more sense to stent arteries in which the atherosclerosis is truly focal, and bypass those with an extensive longitudinal extent of plaque that could rupture anywhere along the vessel, thereby treating the whole artery? That is, a revised SYNTAX score including the vessel plaque volume might improve the selection process. Finally, research studies of new drugs or procedures to treat coronary artery disease would require far fewer patients if they were directed at a select group with a predictable high incidence of acute coronary syndrome.

Studies like that of Versteysen et al. (1), in which the diffuse nature of coronary atherosclerosis is recognized and measured, lay the groundwork for development of a new and more logical way to predict the risk of coronary events. The prescription of personalized, targeted treatment based on CT imaging is a promising direction. Large, well-designed studies will be necessary to learn how to best use this new information.

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Key Words: acute coronary syndrome(s) ■ cardiac computed tomography ■ plaque characteristics quantification ■ prognosis.